REMARKS

Claims 14-20 are pending in this application, and the Examiner rejects all of the pending claims. Upon entry of the instant amendment, claims 14 and 16-22 will be pending.

Rejection under 35 U.S.C. § 103

The Examiner rejects all of the pending claims under 35 U.S.C. § 103. Applicants herein provide new claims 21 and 22 to further clarify certain aspects of the invention. New claim 21 mirrors claim 14 but further recites that the effector molecules are attached to the antibody fragment and the bridging molecule, and are not attached to albumin. No issue of new matter arises by way of this amendment as support can be found in original claims 15 and 20 and page 8, line 23 – page 9, line 3 of the specification. Likewise, new claim 22 mirrors claim 14 differing only in reciting "consisting of" in place of "comprising." No issue of new matter arises by way of this change as "consisting of" is merely more restrictive than "comprising" and thereby defines a subset of the embodiments of claim 14.

A. U.S. Patent No. 6,350,431 in view of Peters

The Examiner rejects claims 14-20 under 35 U.S.C. § 103(a), as allegedly unpatentable over U.S. patent No. 6,350,431 (the '431 patent) in view of Peters (IDS reference "AT") and the known facts disclosed in the specification on page 27, lines 9-13. The Examiner now contends that the '431 patent discloses that albumin can be a linking group and that it also is a polymer and a chelating agent (citing column 21, lines 30-34 and column 46, lines 8-39, and column 50, lines 35-62). Allegedly, the '431 patent teaches that albumin is most preferred (*citing* column 50, lines 58-62) and that the polymeric targeting immunoreagent comprises a metal radinuclide ion, a chelating agent in a linking group of the polymer and an immunoreactive group that is attached through a linking group to the polymer (*citing* column 21, lines 30-50), i.e. a metal ion linked to a chelating agent such as albumin linked through a linker such as hexylene or substituted hexylene to an antibody fragment. The Examiner further contends that one of

ordinary skill in the art at the time the invention was made would have been motivated to use the free cysteine at position 34 of human serum albumin because it is unpaired and would have been motivated to use albumin in the native conformation where an antigen binding antibody fragment rather than an intact antibody because Peters teaches that albumin in native conformation is an abundant serum protein with a half life in circulation of about 19 days, similar to that of the IgG isotype antibody.

The Examiner has not set forth a proper prima facie case of obviousness

Applicants reiterate that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. *In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987).* Moreover, a *prima facie* case of obviousness requires that there be some reasonable expectation of success in making the combination of references.

The '431 patent does not teach or suggest that there is any particular advantage associated with using albumin or hexylene as linkers over any of the other numerous linkers cited. Therefore, the '431 patent provides no motivation to select either or both of these linkers alone or in combination in the same immunoreagent. In particular, the '431 patent provides no motivation to use a hexylene linker to connect an immunoreactive group to an albumin linker. The '431 patent does not teach or suggest that in order for albumin to function as a linker it should retain its native structure. One of ordinary skill in the art in creating the immunoreagent of the '431 patent would have been solely concerned with utilizing the best linker to link components of the immunoreagent together. Each linker in the ' 431 patent is attached to **two** or more other components of the immunoreagent. Even if a skilled artisan had selected albumin as a linker, he would not have been concerned with retaining its native structure in order to use it as a linker to connect two or more components of the immunoreagent. As a result, there would have been no motivation to use position 34 or to consider the Peters reference. Accordingly for the record, Applicants maintain that claims 14-20 are patentable in view of U.S. Patent No. 6,350, 431, Peters and the facts as disclosed in the specification.

The present invention and the '431 patent are not in the same field of invention

Applicants respectfully remind the Examiner that it is a fundamental tenet of the patent law including 35 U.S.C. § 103 that obviousness should be assessed considering the "art to which the subject matter pertains." The present invention is concerned with prolonging the *in vivo* half-life of immunoglobulin fragments by conjugating an antibody fragment to albumin via a bridging molecule. Use of a bridging molecule of between 10 and 20 Å in length as claimed in amended claim 14 prevents the formation of albumin homo-dimers during production of the antibody-albumin fusions. The '431 patent relates to providing light imaging contrast agents, not with prolonging the *in vivo* half-life of immunoglobulin fragments. The '431 patent therefore relates to a completely different field than the present invention and is concerned with solving a different problem. One of ordinary skill in the art would not have considered the teachings of the '431 patent as motivating any structure for prolonging the *in vivo* half-life of immunoglobulin fragments.

The Examiner mischaracterizes the teachings of the '431 patent

Applicants respectfully submit that a number of the allegations made by the Examiner regarding the teachings of the '431 patent are incorrect. First, the Examiner continues to assert that the linking molecules disclosed in the '431 patent range from around 10 angstroms to around 20 angstroms in length (*See*, page 3, paragraph 6 of the Office Action). There simply is no teaching or suggestion in the '431 patent of linking molecules of this length. Likewise, there is no teaching or suggestion in the '431 patent that this length would be desirable to prevent unwanted albumin homodimer formation or to enable an antibody fragment to retain its full binding ability.

Second, the Examiner maintains that "U.S. Patent No. 6,350,431 not only discloses that albumin can be a linking group, but that it is also a polymer and a chelating agent (column 21 at lines 30-34 and column 46, at lines 8-39, column 50 at lines 35-62)." (*See*, bottom of page 3 of the Office Action) In all three instances referred to by the Examiner, albumin is being used as a

linking group between two molecules. The reference to albumin as a polymer cited by the Examiner (column 46 lines 8-39) is in the context of linking groups that may be polymeric (column 46 line 8). The reference to albumin as a chelating agent (column 50 lines 35-62) is also in the context of chelating agents acting as linking groups. Column 48 line 51-52 states the linking group can be a monomer unit and column 49 line 8-9 states that other monomer units which may be used include chelating agents. The specification then goes on to list a host of chelating agents that may be used as linkers.

Third, the Examiner also says that albumin is the *"most preferred"* linking group, polymer or chelating agent in U.S. Patent 6,350,431. (*See*, last line of page 3 of the Office Action) This is not the case. Albumin is more (not most) preferred, along with polyarginine, polylysine and polyhistidine, in situations where the chelating agent is a proteinaceous macromolecule. Referring to Column 50, lines 35 to 57, the '431 patent teaches other suitable and equally preferred chelating agents. Applicants submit that albumin is only one in a long list of chelating agents disclosed as suitable for use as linkers.

Fourth, the Examiner states that the '431 patent discloses "the polymeric targeting immunoreagent comprises a metal radionuclide ion, a chelating agent in a linking group of the polymer and an immunoreactive group which is attached through a linking group to the said polymer (Column 21 at lines 30-50) i.e. a metal ion linked to a chelating agent such as albumin linked through a linker such as hexylene or substituted hexylene to an antibody fragment." (*See*, passage bridging pages 3-4 of the Office Action) The Examiner therefore considers that '431 patent discloses a construct with the following structure:

metal ion – chelating agent (albumin) – hexylene – antibody

The Examiner argues on page 4 of the Office Action that a skilled person reading the '431 patent would have been motivated to use the free cysteine at position 34 of albumin to attach it to the linking molecule (hexylene) in order to retain the native structure of the albumin and to increase the circulating half-life because Peters teaches that albumin has a half-life similar to IgG.

Applicants respectfully submit that this argument ignores the fact that Peters does not teach or suggest that antibody fragments should be conjugated to albumin to increase their half-life. In addition, there is no teaching or suggestion in the '431 patent that there is a need to extend the circulating half-life of an immunoreagent where the targeting agent is an antibody fragment. Furthermore, as albumin is always used in the '431 patent as a connecting linker between two molecules, one of ordinary skill in the art would not have been motivated to look for a single site of attachment to albumin which would retain the native albumin conformation and would therefore not have considered the Peters reference.

Applicants herein provide new claims 21 and 22 to further clarify certain aspects of the invention. New claim 21 mirrors claim 14 but further recites that the effector molecules are attached to the antibody fragment and the bridging molecule, and are not attached to albumin. Support for these amendments can be found in original claims 15 and 20 and page 8, line 23 – page 9, line 3 of the specification. Likewise, new claim 22 mirrors claim 14 differing only in reciting "consisting of" in place of "comprising."

Regarding new claims 21 and 22, the combination of references does not even produce the invention

As set forth above, the '431 patent only uses albumin as a linking molecule between a metal ion and a hexylene linker that is, in turn, linked to an antibody. This structure is not encompassed by new claims 21 and 22. In new claim 21, the effector molecules are not attached to albumin but instead are only attached to the bridging molecule and/or the antibody. The hybrid proteins of new claim 21 have the structure:

albumin – bridging molecule – antibody fragment – effector

or albumin – bridging molecule – antibody fragment
|
effector

or albumin – bridging molecule – antibody fragment - effector
|
effector

In new claim 22, there are no effector molecules. The hybrid proteins of new claim 22 have the structure:

albumin – bridging molecule – antibody fragment

In contrast, the '431 patent teaches using albumin as a linker between two molecules. There is no teaching or suggestion of any other use. In the hybrid proteins of claims 21 and 22, albumin is not used as a linker between two molecules. Instead, albumin is used to increase the half-life of the antibody fragment to which it is attached.

Applicants reiterate that the '431 patent only teaches albumin as a linker molecule. One of ordinary skill in the art would not have been motivated to look for a single site of attachment to albumin that would retain the native albumin conformation and would therefore not have considered the Peters reference.

Certain sizes of the linker molecules are separately patentable

The Examiner previously maintained that the linking molecules disclosed in the '431 patent are from around 10Å to around 20Å in length. Applicants respectfully traverse. Respectfully, the '431 patent simply does not teach or suggest linkers of this length. Likewise, the '431 patent does not teach or suggest that this length is desirable to prevent unwanted

albumin homodimer formation or to enable an antibody fragment to retain its full binding ability. Hence, in the interest of advancing prosecution and securing rapid allowance of a patent directed to these particular embodiments, Applicants herein combine the language of claims 15 and 14 to recite linking molecules of this particular size.

B. U.S. patent No. 4,751,286 in view of U.S. patent No. 4,749,570, Peters (IDS reference "AT")

The Examiner rejects claims 14 and 17-20 under 35 U.S.C. § 103(a), as being obvious over U.S. patent No. 4,751,286 (the '286 patent) in view of U.S. patent No. 4,749,570 (the '570 patent), Peters (IDS reference "AT") ('570 patent) and the known facts disclosed in the specification on page 27, lines 9-13. The Examiner now asserts that the '286 patent teaches a compound comprising a bridging agent (optionally linked to a drug, dye or label capable of bridging reduced or unpaired sulfhydral groups of a protein. The Examiner contends that the '286 patent teaches an example of a particular bridging agent, crabescein, and that insertion of the bridging agent across the reduced disulfide bonds in fab fragments of antibodies or the fab region of intact antibodies can alter the affinity (citing column 8, lines 33-46). The Examiner adds that the '286 patent teaches that when the protein is an intact antibody, the crabescein bridging agent is inserted below the hinge region, a region not present in a fab fragment of an antibody, and that structural analyses of IgGs have shown that unlike the region of the interchain disulfide bond in the Fab segment, below the hinge region there is little interchain interaction between the heavy chains and hence a space in this region large enough for a bridging molecule the size of crabescein (citing column 6, lines 62-67). The Examiner further contends that the '570 patent teaches albumin-F(ab')2 antibody fragments to reduce immunogenicity (citing Table II at column 7, Example 5). The Examiner says that one of ordinary skill in the art would have been motivated to use a bridging agent capable of bridging reduced or unpaired sulfhydral groups in a protein, and the agent having the expected property of bridging reduced or unpaired sulfhydral groups of one protein to another protein, the size of the agent chosen from the purpose for which it is used as disclosed by the '286 patent to make a fab-albumin-therapeutic agent conjugate using a bridging agent of the general structure disclosed by the '286 patent or a

F(ab')2-albumin-therapeutic agent conjugate using crabescein (which inserts at residue cys-229 that is present in F(ab')2 fragments). The Examiner further contends that one of ordinary skill in the art at the time of the invention would have been motivated to use the free cysteine at position 34 of human serum albumin taught by Peters because it is unpaired and to use albumin in native conformation where an antigen-binding antibody fragment rather than an intact antibody was being used because Peters teaches that albumin in native conformation is an abundant serum protein with a half life in circulation of about 19 days, similar to that of the IgG isotype antibody. The Examiner acknowledges that claims reciting a linker length of around 10 to 20 angstroms in length are not included in the rejection.

In the interest of advancing prosecution and securing rapid allowance of a patent directed to embodiments where the linker length is the noted particular length, Applicants herein combine the language of claims 15 and 14 so that the broadest claim is now directed to the embodiments that the Examiner acknowledges are free of this rejection.

As noted previously and for the record, the '286 patent teaches linking a monoclonal antibody to a drug, label or dye. The antibody conjugate is a whole IgG, not an antibody fragment. A drug, label or dye is attached to the whole IgG molecule. As Applicant previously explained, the '286 patent does not teach or suggest certain features of Applicant's invention. For example, the '286 patent does not teach or suggest the possibility of using antibody fragments. Furthermore, the use of antibody fragments would contradict the rationale for using whole IgG (column 5, line 55), since whole IgG was chosen because 1) it has been shown to have a limited number of accessible disulfide bonds and 2) the disulfides of the protein can be reduced without dissociating the heavy and light chains. Furthermore, the '286 patent does not teach or suggest attaching albumin to the IgG. In fact, the '286 patent does not even disclose albumin. The drug, label or dye is attached via a bridging structure within the IgG between two cysteines that are normally in a disulfide linkage with each other. The purpose of this approach is to retain the natural antibody structure. For example, the '286 patent teaches inserting crabescein below the hinge region. This region was chosen as there is little interchain interaction between heavy

chains, unlike the region of the interchain disulfide bond in the Fab segment. Thus, there was sufficient space for crabescein to reside within the normal antibody structure (column 6, lines 62-67). The third disulfide bond was used for insertion of crabescein, the most distal from the Fab arms (column 7, line 1).

Even if a skilled artisan had conjugated albumin to the conjugate of the '286 patent, there is no motivation provided in the '570 patent to maintain the native structure of the albumin carrier by non-disruption of intrachain disulfide bonds. The '570 patent describes a process for chemical linkage of a therapeutic agent and a targeting agent to a carrier albumin which in most cases utilizes a cross-linking agent such as glutaraldehyde, sodium periodate and water soluble carbodiimide (column 3, line 47). There is no teaching or suggestion that bridging structures could be used or that it would be desirable to retain albumin in its native form. The '570 patent only teaches direct conjugation. In fact, column 6, line 1 states that the conditions used for cross-linking should be such that the biological activity of the therapeutic agent and the binding specificity of the targeting agent are maintained. There is no teaching or suggestion of a need to maintain the native structure of the albumin. The conjugates produced were shown to be non-immunogenic demonstrating that there were no issues with the albumin or the cross-linking used that would motivate the person skilled in the art to seek alternatives. Likewise, there is no teaching or suggestion for using albumin to prolong the half-life of antibodies or antibody fragments.

In the absence of any motivation to use albumin in its native form or to look for alternative conjugation methods, the skilled artisan would have no motivation to look at the Peters reference or to single out the cysteine of position 34 as a site of attachment. Any allegation to the contrary is no more than hindsight reasoning, and hindsight analysis has long been rejected as an improper basis for a rejection under 35 U.S.C. § 103.

Furthermore, one of ordinary skill in the art would have had no motivation to look at the '431 patent wherein albumin is only found in a long list of possible linkers. No explicit teaching

or suggestion of the desired linker length of 10 to 20 angstroms is present in the '431 patent. Likewise, there is no teaching or suggestion that this length would be desirable to prevent unwanted albumin homodimer formation or to enable an antibody fragment to retain its full binding ability as disclosed in the present application.

Accordingly, Applicants submit that claims 14 and 17-20 are patentable over U.S. Patent No. 4,751,286 in view of U.S. patent No. 4,749,570, Peters IDS reference "AT" and the known facts disclosed in the specification on page 27, lines 9-13.

Fees

A check in the amount of $110.00 for a one-month extension of time is enclosed. No other fees are believed required by this response, but if any other fees are found to be required, the Commissioner is hereby authorized to charge any fees, or credit any overpayment, to Deposit Account No. 11-1153.

Conclusion

Applicants believe that the outstanding rejections based on 35 U.S.C. § 103(a) have been overcome by the amendments presented above. Thus, reconsideration and withdrawal of the outstanding grounds of rejection, and early allowance of the claims as amended is believed to be in order and is courteously solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned at the number listed below, so that prosecution of the application may be expedited.

Respectfully submitted,

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